L1TD1 Is a Marker for Undifferentiated Human Embryonic Stem Cells.

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Authors: Raymond Ching-Bong Wong, Abel Ibrahim, Helen Fong, Noelle Thompson, Leslie F Lock, Peter J Donovan

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Public Summary:
Human embryonic stem cells (hESC) are stem cells capable of differentiating into cells representative of the three primary embryonic germ layers. There has been considerable interest in understanding the mechanisms regulating stem cell pluripotency, which will ultimately lead to development of more efficient methods to derive and culture hESC. In particular, Oct4, Sox2 and Nanog are transcription factors known to be important in maintenance of hESC. However, many of the downstream targets of these transcription factors are not well characterized. Furthermore, it remains unknown whether additional novel stem cell factors are involved in the establishment and maintenance of the stem cell state. Here we show that a novel gene, L1TD1 (also known as FLJ10884 or ECAT11), is abundantly expressed in undifferentiated hESC. Differentiation of hESC results in the rapid down-regulation of L1TD1 expression. Furthermore, our results show that L1TD1 is enriched in the purest population of hESC. Altogether, our results provide evidence that L1TD1 is a downstream target of Nanog. Taken together, our results suggest that L1TD1 is a downstream target of Nanog and represents a useful marker for identifying undifferentiated hESC.

Scientific Abstract:
BACKGROUND: Human embryonic stem cells (hESC) are stem cells capable of differentiating into cells representative of the three primary embryonic germ layers. There has been considerable interest in understanding the mechanisms regulating stem cell pluripotency, which will ultimately lead to development of more efficient methods to derive and culture hESC. In particular, Oct4, Sox2 and Nanog are transcription factors known to be important in maintenance of hESC. However, many of the downstream targets of these transcription factors are not well characterized. Furthermore, it remains unknown whether additional novel stem cell factors are involved in the establishment and maintenance of the stem cell state. METHODOLOGY/PRINCIPAL FINDINGS: Here we show that a novel gene, L1TD1 (also known as FLJ10884 or ECAT11), is abundantly expressed in undifferentiated hESC. Differentiation of hESC via embryoid body (EB) formation or BMP4 treatment results in the rapid down-regulation of L1TD1 expression. Furthermore, populations of undifferentiated and differentiated hESC were sorted using the stem cell markers SSEA4 and TRA160. Our results show that L1TD1 is enriched in the SSEA4-positive or TRA160-positive population of hESC. Using chromatin immunoprecipitation we found enriched association of Nanog to the predicted promoter region of L1TD1. Furthermore, siRNA-mediated knockdown of Nanog in hESC also resulted in downregulation of L1TD1 expression. Finally, using luciferase reporter assay we demonstrated that Nanog can activate the L1TD1 upstream promoter region. Altogether, these results provide evidence that L1TD1 is a downstream target of Nanog. CONCLUSION/SIGNIFICANCE: Taken together, our results suggest that L1TD1 is a downstream target of Nanog and represents a useful marker for identifying undifferentiated hESC.

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